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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,560	02/09/2001	Marianne Harboe	58982.000002	6162

7590 09/12/2005

Stanislaus Aksman
Hunton & Williams
Suite 1200
1900 K Street, N.W.
Washington, DC 20006

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,560	HARBOE, MARIANNE	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,9-14,16-18,29-31,35,36,39,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,9,12-14,16-18,29-31,39,42 and 43* is/are rejected.

7)☒ Claim(s) *10,11,35 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5100

DETAILED ACTION

Status of the Application

[1] The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are pending in the application.

[3] Applicants' amendment to the claims, filed on 6/21/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicants' amendment to the specification, filed 6/21/2005, is acknowledged.

[5] Applicants' arguments filed on 6/21/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, First Paragraph

[7] The written description rejection of claims 9, 29-31, and 39 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue: 1) the specification adequately describes the genus of media comprising chymosin and glucoamylase activities; 2) the materials for providing a medium comprising chymosin and glucoamylase activities

were widely available at the time of the invention; and 3) the Office action fails to set forth a reasonable basis for doubting the truth of the disclosure.

Applicants' argument is not found persuasive. Claim 9 limits the genus of media comprising chymosin and glucoamylase activities to being derived from the cultivation of (in relevant part) an animal species and a plant species. Claims 29-31 and 39 limit the chymosin activity to being "derived from" recited mammalian species. At p. 7 of applicants' response filed 10/9/02, the term "derived from" was clarified by applicants to mean "to obtain from a source of origin." In accordance with applicants' intended meaning of "derived from," the examiner has interpreted claims 29-31 and 39 as meaning that the chymosin activity in the medium comprising chymosin and glucoamylase activities is obtained from the mammalian sources recited in the claims. Thus, claims 29-31 and 39 are interpreted as meaning that the medium comprising chymosin and glucoamylase activites of claims 29-31 and 39 is obtained from the recited mammalian species as recited in claims 29-30 and 39.

While it is acknowledged that the specification discloses representative species of media comprising chymosin and glucoamylase activities, these media appear to be obtained from microbial sources that recombinantly express chymosin and either recombinantly express or endogenously express glucoamylase. The disclosed media do not appear to be obtained from an animal species, a plant species, or a mammalian species. While the examiner acknowledges that certain ruminant species, *e.g.,* bovine, endogenously express chymosin, there is no evidence of record that these species can endogenously express glucoamylase and the examiner can find no evidence in the prior

art that these species can endogenously express glucoamylase. Further, there is no evidence of record of these species recombinantly expressing glucoamylase. It is the examiner's position that the disclosed representative species of microbially-produced media comprising chymosin and glucoamylase activities fail to represent the genus of recited media that are obtained from or that are derived from the culture of an animal species, a plant species, or a mammalian species. In this case, the specification fails to disclose even a single representative species of such media that are obtained from or that are derived from the culture of an animal species, a plant species, or a mammalian species. In the absence of a representative number of species of the genus of recited media that are obtained from or that are derived from the culture of an animal species, a plant species, or a mammalian species, the specification fails to adequately describe the claimed invention.

[8] The scope of enablement rejection of claims 9, 29-31, and 39 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue that the evidence of enablement of record, pointing to the disclosed working examples and the reference of Ward et al., has been completely ignored by the examiner and that without consideration of all disclosed examples, the rejection must be withdrawn.

Applicants' argument is not found persuasive. As noted above, claims 9, 29-31, and 39 encompass media comprising chymosin and glucoamylase activities obtained from animal, plant, and mammalian species. While it is acknowledged that the

specification discloses working examples of media comprising chymosin and glucoamylase activities, these media appear to be obtained *only* from microbial sources that recombinantly express chymosin and either recombinantly express or endogenously express glucoamylase. The specification fails to disclose even a single working example of an animal, plant, or mammalian species from which media can be obtained that comprises chymosin and glucoamylase activities, particularly as there is no evidence of record that animal, plant, and mammalian species endogenously express glucoamylase or can be genetically engineered to recombinantly express glucoamylase such that the desired medium can be obtained from these species. Further, neither the specification nor the prior art provides guidance for obtaining such media and without the necessary guidance and expectation that glucoamylase activity is present in an animal, plant, and/or mammalian species, it is highly unpredictable as to whether one of skill in the art can successfully obtain such media. Thus, the skilled artisan is left to experiment, without any particular guidance, in order to determine if such a medium can be obtained from an animal, plant, and/or mammalian species.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high level of unpredictability, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

[9] The rejection of claim(s) 1, 5-6, 9, 12-14, 16-18, and 42-43 under 35 U.S.C. 103(a) as being unpatentable over Ward et al. in view of Larsen et al. is maintained for the reasons of record and the reasons stated below.

Applicants argue the disclosed reduction in glucoamylase activity occurs over a pH range that is not taught by Larsen and will not necessarily result from practicing the method of Larsen. According to applicants, the Office action fails to support the determination that the inherent characteristic necessarily flows from the prior art and as a result, the combination of references does not teach every limitation of the claims.

Applicants' argument is not found persuasive. As noted in a previous Office action, Larsen teaches that chymosin activity is retained even at a pH as low as 0.5 (p. 10, bottom). The reference of Larsen is cited for it's showing that, if one were to reduce the pH of a medium below 2.0, chymosin would retain its catalytic activity. This is also evidenced by Ward, who teaches that pseudochymosin is "fairly stable" at a pH below 3 (p. 435, left column, middle). Larsen supports an expectation of success that if one were to practice the method of Ward, *i.e.,* taking the culture medium comprising a glucoamylase-chymosin fusion protein and, instead of lowering the pH of the medium to 2.0 as taught by Ward, one were to lower the pH of the medium to below 2.0, *e.g.,* a pH of 0.5 to 1.99, chymosin would retain its catalytic activity. As noted in the previous Office action, the disclosure teaches that treatment at the recited pH range for a time of 0.1 minutes to 48 hours will achieve the recited level of deactivated glucoamylase, while maintaining the desired level of chymosin activity. It is acknowledged that neither Ward nor Larsen teaches treating the respective medium at low pH specifically for reducing

glucoamylase activity. However, the examiner maintains the position that by practicing the method of Ward at a lower pH, *e.g.,* pH 1.99, one would inherently achieve the recited reduction in glucoamylase activity, while maintaining the desired level of chymosin activity. The reference of Ward teaches treating the medium comprising chymosin and glucoamylase activities for 30 minutes, a period of time that falls within the disclosed 0.1 minute to 48 hour time period. In view of the disclosure, it necessarily flows that treatment of the medium at a pH as low as 0.5 for 30 minutes would achieve the recited level of deactivated glucoamylase, while maintaining the desired level of chymosin activity.

Applicants argue there is no motivation to combine the references as they do not teach any specific result that can be achieved by lowering the pH of the medium below 2.0. Applicants argue the examiner's rationale for combining the references, *i.e.,* to determine whether pH values lower than 2.0 increases the cleavage of the fusion protein, is an "obvious to try" analysis.

Applicants' argument is not found persuasive. The examiner maintains that there is proper motivation to combine the cited references. MPEP 2144 states that equivalency or optimization of ranges can be used as a rationale for an obviousness rejection. Ward teaches that using a "low pH" favors cleavage of the fusion protein into chymosin and glucoamylase moieties. Although Ward does not define what pH value(s) are encompassed by "low pH," one of ordinary skill in the art would clearly recognize that, for the purpose of cleaving the fusion protein of Ward, treating a medium comprising a glucoamylase-chymosin fusion protein at pH 1.99 is the equivalent of

treating a medium at pH 2.0, particularly as there is only a difference in the pH values of 0.01. Alternatively, one of ordinary skill in the art would recognize that practicing the method of Ward at a "low pH" by lowering the pH to 1.99 instead of 2.0 is merely using a pH within a workable range of low pH values (that are known to maintain active chymosin as disclosed by Larsen) to achieve activation of a catalytically active chymosin.

Applicants argue that reducing the pH below 2.0 after activating the chymosin at pH of 2.0 is an additional step that is not suggested by the prior art of record and would be contrary to Ward's disclosure of raising the pH to 4.5 following treatment of the medium at a pH of 2.0.

Applicants' argument is not found persuasive. The examiner has not indicated that the combination of references teaches that one of ordinary skill in the art would modify the method of Ward to treat the medium at pH 2.0 and include the extra step of reducing the pH of the medium below 2.0. Instead, one would follow the method of Ward and, instead of lowering the pH to 2.0, would lower the pH to below 2.0. In other words, after harvesting the medium, one of ordinary skill in the art would reduce the culture medium to a pH below 2.0 *directly* and then raise the medium to a pH of 4.5 in accordance with the teachings of Ward.

Applicants argue the use of an optimization rationale for finding inherency based on the cited references is ineffective because, according to applicants, the inherency is based on what would result due to optimization of conditions, not what is necessarily present in the prior art.

Applicants' argument is not found persuasive. The reference of Ward teaches that the medium used for culturing *Aspergillus niger* var. *awamori* transformed with a plasmid encoding a glucoamylase-chymosin fusion protein had a pH of at least 5 (p. 439, right column, bottom) and the pH of that medium, following culturing of the glucoamylase-chymosin fusion protein was reduced to 2.0. Thus, initially the medium comprising the glucoamylase-chymosin fusion protein was at pH 5 and was treated with an acid to lower the pH to 2. Using a rough approximation of the date presented in the specification, it is the examiner's position that the desired reduction in glucoamylase activity, while maintaining the desired level of chymosin activity is achieved using the method of Ward. Example 2 of the instant specification teaches that the medium of *Aspergillus niger* var. *awamori* transformed with a plasmid encoding a glucoamylase-chymosin fusion protein cultured at a pH of 5.6 had glucoamylase activity of 30,619 U/mL and at pH 1.8 had glucoamylase activity of 4,020 U/mL (p. 13, top). Figure 1 of the specification shows that the remaining glucoamylase activities following treatment of a medium comprising a glucoamylase-chymosin fusion protein at pH 1.8 and 2.0 are substantially similar. Thus, by extrapolation of the results of Example 2 and Figure 1 as described above, one would reasonably expect that the remaining glucoamylase activity of the medium as described in Example 2 treated at pH 2.0 would be substantially similar to the glucoamylase activity of 4,020 U/mL at pH 1.8. One of ordinary skill in the art would recognize that one practicing the method of Ward would achieve the reduction in glucoamylase activity to the recited level.

Also, it is noted that applicants' specification indicates that a time period of as little as 0.1 minute at a pH lowered to, *e.g.,* 1.99, is sufficient to achieve the recited reduction in glucoamylase activity while maintaining the recited level of chymosin activity (p. 7, middle). Also, dependent claim 18 limits the time period to as little as 0.1 minutes at a pH of 1.99. The method of Ward teaches treating the medium at a pH of 2 for 30 minutes, which is a significantly longer time period than the 0.1 minute time range disclosed in the specification. The results of Figure 1 of the specification show that the difference in reduction of glucoamylase activity at pH 1.99 and pH 2 is negligible. Thus, one of ordinary skill in the art would expect that by lowering the pH of a medium from 5 to 2 and maintaining the pH at 2 for a time of 30 minutes would achieve a nearly identical reduction in glucoamylase activity by lowering the pH of a medium from 5 to 1.99 for a time period greater than 0.1 minute, which according to the disclosure, would achieve inactivation of at least 50% of the glucoamylase activity.

Further, Ward provides evidence that at least 85% chymosin activity is maintained by lowering the pH to 2 by teaching that, by lowering the pH of the medium from 5 to 2 increased chymosin activity by 5-fold (p. 438, left column, bottom).

At least for the reasons stated above, the inherency argument is based on what is necessarily present in the prior art, not what would result due to optimization of conditions.

Conclusion

[10] Status of the claims:

- Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are pending.
- Claims 1, 5-6, 9, 12-14, 16-18, 29-31, 39, and 42-43 are rejected.
- Claims 10-11 and 35-36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs and alternate Fri, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656